BRIEF COMMUNICATION

Male Breast Cancer Incidence Among Atomic Bomb Survivors

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To learn more about the role of ionizing radiation in the development of male breast cancer, we evaluated male breast cancer incidence among 45 880 male members of the Life Span Study cohort of Japanese atomic bomb survivors. Male breast cancers, diagnosed between January 1, 1958, and December 31, 1998, were identified through the Hiroshima and Nagasaki Tumor Registries. Nine male breast cancers were diagnosed among exposed Life Span Study members (crude rate = 1.8 per 100 000 person-years), and three were diagnosed among nonexposed cohort members (crude rate = 0.5 per 100 000 person-years). A statistically significant dose–response relation was observed (excess relative risk per sievert = 8, 95% confidence interval = 0.8 to 48; *P* = .01). Our finding of a statistically significant association between ionizing radiation and male breast cancer incidence adds to the very limited information that shows an association between radiation exposure and an increased risk of male breast cancer. [J Natl Cancer Inst 2005;97:603–5]

Male breast cancer is relatively infrequent throughout the world and generally accounts for less than 0.5% of cancers in males and about 1% of all breast cancers *(1)*. In Japan, however, the incidence of both male and female breast cancer is particularly low *(1)*. The incidence of male and female breast cancers differs in terms of age patterns, with the age of onset being greater for male breast cancer patients than for female breast cancer patients *(2)*. Anatomically, the male breast is similar to an undeveloped breast of a prepubescent girl. It consists primarily of fatty and fibrous tissues without many ducts or lobular elements *(3)*. Decreasing levels of androgens in older men can result in some ductal proliferation occurring in their breasts.

Because of the rarity of breast cancer in males, the etiology of this disease is not well described, but some risk factors are similar to those observed for female breast cancer—e.g., family history of breast cancer, higher social class, and Jewish religion *(4)*. Ionizing radiation is a well-known risk factor for female breast cancer *(5,6)*. Among atomic bomb survivors, the incidence of female breast cancer increases linearly with radiation dose, with age at exposure or attained age modifying the radiation risk *(6)*. Much less is known about radiation as a risk for male breast cancer, although based on personal interviews, a history of prior diagnostic or therapeutic medical radiation exposure was associated with male breast cancer in a large population-based case–control study conducted in the United States *(7)*. An increased risk of male breast cancer was found 20 years or more after exposure, but risk appeared to diminish 30–40 years after exposure. To learn more about the role of ionizing radiation in the development of male breast cancer, we examined male breast cancer incidence among members of the well-established Life Span Study cohort of atomic bomb survivors *(6,8)*.

Male breast cancers were identified through the Hiroshima and Nagasaki Tumor Registries and other medical records related to members of the Life Span Study. Because the tumor registries were established in 1958, analyses were restricted to Life Span Study members who were alive and cancer-free at that time. Two study pathologists (T. Ikdea and S. Tokuoka) reviewed pathology specimens or reports and classified diagnoses according to the World Health Organization histologic criteria *(9)*. Individual breast doses in sieverts (Sv) were computed with DS02, the new Life Span Study dose estimation system *(10)*. The study population was 45 880 male Life Span Study members who met the study criteria: 32 411 who received a known radiation dose, 2978 who received appreciable doses but for whom doses could not be computed because of complicated or unknown shielding, and 10 491 Hiroshima or Nagasaki residents who were not in the cities at the time of the bombings. Cancer incidence follow-up was through December 31, 1998. Risks were estimated with simple age-adjusted excess relative risk models *(8,11)*. Hypothesis tests and confidence intervals were based on maximum-likelihood methods *(12)*.

Between January 1, 1958, and December 31, 1998, nine male breast cancers were diagnosed among exposed Life Span Study cohort members (crude rate = 1.8 per 100 000 person-years), including seven cases among survivors with known dose and two among members with unknown dose. Three male breast cancers were diagnosed among cohort members who were not in city at the time of the bombings (crude rate = 0.5 per 100 000 person years). Although detailed dose–response analyses were not possible with only 12 cases, a radiation effect was evident (Table 1), and a statistically significant age-adjusted trend with dose was observed (*P* = .01). The excess relative risk per sievert was estimated as 8 (95% confidence interval = 0.8 to 48), but, as indicated by the wide confidence interval, the risk estimate was imprecise.

Age at diagnosis among male breast cancer patients ranged from 42 to 88 years. The mean age was 67 years, which is 7 years older than the mean age for female breast cancer patients in this cohort. Only one patient was diagnosed when younger than age 50 years

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Table 1. Crude male breast cancer rates by breast dose in this study

Radiation dose to the breast, Sv	Rate of male breast cancer per 100 000 person-years	No. of cases	Person-years
<0.005	0.5	3	604 097
0.005–0.5	1.3	5	375 668
0.5–1	3.7	1	27 119
>1	3.0	1	33 394
Unknown*	2.8	2	71 213

*These survivors were exposed in concrete buildings located approximately 1500 m from the Nagasaki hypocenter. Their doses are not estimated because of the complexity of the shielding. The mean breast dose estimates for other survivors at this distance is 0.5 Sv.

(Table 2). All of the cancers occurred 25 or more years after exposure; however, it should be noted that, because the cancer registries were established in 1958, there was no follow-up for the first 13 years after exposure. One cancer was diagnosed among the exposed survivors and one was diagnosed among the nonexposed subjects during the last 5 years of follow-up. Three breast cancer patients were exposed to radiation from the bombings at or before age 15 years compared with about 1.5 patients expected, suggesting that early age at exposure might be a risk modifier.

Pathology slides were reviewed by the study pathologists from nine patients, and pathology records were reviewed for the other three patients. All but one tumor was invasive ductal carcinoma (Table 2). Metastases to the lymph nodes were found in four patients. Radiation dose was not associated with pathologic diagnosis, histologic subtype, or lymphatic invasion, but the small number of patients precludes reaching any definitive conclusions.

In the largest study of male breast cancer to evaluate ionizing radiation as a risk factor, a trend for an increasing risk of breast cancer with an increasing number of self-reported x-ray examinations was observed, which was statistically significant for exams performed between 1933 and 1963 *(7)*. After radiation therapy, a marginally elevated risk was observed for men first treated before 1954, and the risk was somewhat higher when the location of the treatment field resulted in exposure to the breast. Because the number of radiation-exposed individuals was limited and doses were not available, evaluation of age and time effects was limited: Age at radiation exposure was not statistically significantly related to breast cancer risk, and risk was increased only 20–35 years after radiation exposure. The occurrence of male breast cancer has been reported infrequently in cohorts of radiation-exposed subjects. Because of the lack of radiation doses in several of the studies and the very small number of cases in all of them, meaningful quantified risks could not be estimated *(13–17)*.

The long latency seen in our study was consistent with that previously reported *(7)*; however, excess risks were still apparent 40 years or more after exposure. It is of interest that, in the Life Span Study, radiation-associated breast cancers were observed earlier among women *(6)* than among men (this study), but this difference could be because of the few patients with male breast cancers rather than biologic variation.

Because male breast cancer is a rare disease, few cases were seen in this 40-year follow-up of a large cohort. However, the results clearly show an association between exposure to external radiation and the occurrence of male breast cancer. This study sheds some light on age and time patterns of risk, but, because of the small numbers of patients, the radiation risks could not be quantified precisely.

Table 2. Description of male breast cancer cases in this study

Radiation dose to the breast, Sv	Age at exposure, y	Age at diagnosis, y	Cancer diagnosis	Tumor subtype*
0	13	64	Ductal	Papillary tubular
0	32	77	Ductal	Scirrhous
0	45	69	Ductal	Papillary tubular
0.005	15	51	Ductal	Solid tubular
0.098	29	74	Ductal	Solid tubular
0.225	4	42	Ductal with predominant intraductal	Papillary tubular
0.331	41	69	Mucinous	Mucinous
0.365	22	66	Ductal	Papillary tubular
0.529	46	81	Ductal	Papillary tubular
4.04	8	59	Ductal	Solid tubular
Unknown	30	70	Ductal	—
Unknown	46	88	Ductal	—

*— = not available.

References

(1) Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents. Vol VIII. IARC Scientific Publications No. 155, Lyon (France): International Agency for Research on Cancer; 2002.

(2) Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast cancer in men. A population-based study. Cancer 2004;101:51–7.

(3) Newman J. Breast cancer in men and mammography of the male breast. Radiol Technol 1997;69:17–28.

(4) Levi F, Lucchini F, La Vecchia C. Epidemiology of male breast cancer. Eur J Cancer Prev 2002;11:315–8.

(5) UNSCEAR. Sources and effects of ionizing radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2000 Report to the General Assembly, with Scientific Annexes, Vol II: Effects. New York (NY): United Nations; 2000.

(6) Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I, et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. Radiat Res 2003;160:707–17.

(7) Thomas DB, Rosenblatt K, Jimenez LM, McTiernan A, Stalsberg H, Stemhagen A, et al. Ionizing radiation and breast cancer in men (United States). Cancer Causes Control 1994;5:9–14.

(8) Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: solid cancer and noncancer disease mortality: 1950-1997. Radiat Res 2003;160:381–407.

(9) Azzopardi JG, Chepick OF, Hartmann WH, Jafary NA, Llombart-Bosch A, Ozzello L, et al. The World Health Organization histological typing of breast cancer, second edition. Am J Clin Pathol 1982;78:806–19.

(10) Preston DL, Pierce DA, Shimizu Y, Cullings HC, Fujita S, Funamoto S, et al. Effect of atomic bomb survivor dosimetry changes on cancer mortality risk estimates. Radiat Res 2004;62:377–89.

(11) Preston DL, Lubin J, Pierce D, McConney M. Epicure Users Guide. Hirosoft International Corporation, Seattle (WA); 1993.
(12) Cox DR, Hinkley DV. Theoretical statistics. London, Chapman and Hall; 1974.
(13) Weiss HA, Darby SC, Doll R. Cancer mortality following X-ray treatment for ankylosing spondylitis. Int J Cancer 1994;59:327–38.
(14) Doody MM, Mandel JS, Lubin JH, Boice JD Jr. Mortality among United States radiologic technologists, 1926-90. Cancer Causes Control 1998;9:67–75.
(15) Sont WN, Zielinski JM, Ashmore JP, Jiang H, Krewski D, Fair ME, et al. First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. Am J Epidemiol 2001;153:309–18.
(16) Berrington A, Darby SC, Weiss HA, Doll R. 100 Years of observation on British radiologists: mortality from cancer and other causes 1897–1997. Br J Radiol 2001; 507–19.
(17) Shilnikova NS, Preston DL, Ron E, Gilbert ES, Vassilenko EK, Romanov SA, et al. Cancer mortality risk among workers at the Russian nuclear complex Mayak. Radiat Res 2003;159:787–98.

Notes

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